Claims

1. (original) A method of sequencing a sample nucleic acid molecule, comprising:

exposing the sample nucleic acid molecule to an oligonucleotide primer and a polymerase in the presence of a mixture of nucleotides, wherein the polymerase and the nucleotides each comprise a fluorophore which emits a signal corresponding to addition of a particular nucleotide as each nucleotide is incorporated into a synthesized nucleic acid molecule which is complementary to the sample nucleic acid molecule; and

detecting the signal as each nucleotide is incorporated into the synthesized nucleic acid molecule.

2. (original) The method of claim 1, wherein the nucleic acid is DNA and the polymerase is a DNA or RNA polymerase.

3. (original) The method of claim 1, wherein the nucleic acid is RNA and the polymerase is reverse transcriptase.

4. (original) The method of claim 1, wherein the polymerase is a Klenow fragment of DNA polymerase I.

5. (original) The method of claim 1, wherein an emission signal from the fluorophore of the polymerase excites the fluorophore of one of the nucleotides, generating a unique emission signal for each nucleotide as the nucleotide is added to the synthesized nucleic acid molecule and wherein a sequence of the emission signals is detected and converted into a nucleic acid sequence.

6. (original) The method of claim 5, wherein the unique emission signal is converted into a signal for a specific nucleotide in a nucleic acid sequence.

7. (original) The method of claim 5, wherein the unique emission signal is generated by the group consisting of luminescence resonance energy transfer (LRET) and fluorescent resonance energy transfer (FRET).

8. (original) The method of claim 1, wherein the fluorophore of the polymerase is a donor fluorophore and the fluorophore of each nucleotide is an acceptor fluorophore.

9. (original) The method of claim 8, wherein each of the acceptor fluorophores is stimulated by an emission from the donor fluorophore, but each of the acceptor fluorophores emits a unique emission signal.

10. (original) The method of claim 9 further comprising exciting the donor fluorophore to emit an excitation signal which stimulates the acceptor fluorophore to emit the unique signal corresponding to addition of a particular nucleotide.

11. (original) The method of claim 10, wherein the donor fluorophore is green fluorescent protein (GFP).

12. (original) The method of claim 10, wherein the acceptor fluorophores are BODIPY, fluorescein, rhodamine green, and Oregon green or derivatives thereof.

13. (original) The method of claim 9, wherein the donor fluorophore is excited by a luminescent molecule.

14. (original) The method of claim 13, wherein the donor fluorophore is GFP and the luminescent molecule is aequorin.

15. (original) The method of claim 9, wherein the wherein the donor fluorophore is a luminescent molecule.

16. (original) The method of claim 15, wherein the wherein the luminescent molecule is aequorin.

17. (original) The method of claim 1, wherein the polymerase is a GFP-polymerase.

18. (original) The method of claim 8, wherein the donor fluorophore and one of the acceptor fluorophores comprise a FRET pair selected from the group consisting of GFP mutant H9 and its derivatives, H9-40, tetramethylrhodamine, Lissamine™, Texas Red and naphthofluorescein.

19. (original) The method of claim 1, further comprising fixing the polymerase to a substrate.

20. (original) The method of claim 19, wherein the polymerase is fixed to the substrate by a linker molecule comprising a polymerase component and a substrate component.

21. (original) The method of claim 20, wherein the linker is selected from the group consisting of streptavidin-biotin, histidine-Ni, S-tag-S-protein, and glutathione-glutathione-S-transferase (GST).

22. (original) The method of claim 1, further comprising fixing the sample nucleic acid molecule or the oligonucleotide primer to a substrate.

23. (original) The method of claim 1, further comprising performing a plurality of sequencing reactions substantially simultaneously, and detecting the signals from the plurality of sequencing reactions.

24. (original) The method of claim 23, wherein a plurality of polymerases, sample nucleic acid molecules, or oligonucleotide primers are fixed directly or indirectly to the substrate

in a predetermined pattern, and detecting the signal further comprises correlating the signal with a nucleic acid molecule corresponding to a predetermined position within that pattern.

25. (original) The method of claim 24, wherein the polymerases, sample nucleic acid molecules, or oligonucleotide primers are fixed to the substrate in the predetermined pattern in channels which have been etched in an orderly array.

26. (original) The method of claim 24, wherein the polymerases, sample nucleic acid molecules, or oligonucleotide primers are fixed to the substrate in the predetermined pattern by micropipetting droplets onto a substrate.

27. (original) The method of claim 24, wherein the micropipetting droplets onto a substrate is performed manually or with an automated arrayer.

28. (original) The method of claim 5, wherein the unique emission signals are detected with a charged-coupled device (CCD) camera and converted into the nucleic acid sequence.

29. (original) The method of claim 5, wherein the unique emission signals are stored in a computer readable medium.

30. - 34. (canceled)

35. (previously presented) The method of claim 1 wherein the sample nucleic acid is attached to a substrate.

36. (previously presented) The method of claim 1, wherein the oligonucleotide primer is attached to a substrate.

37. -45 (canceled)

46. (previously presented) The method of claim 23, wherein a plurality of polymerases, sample nucleic acid molecules, or oligonucleotide primers are embedded into a three-dimensional gel matrix.

47. (previously presented) The method of claim 46, wherein the three-dimensional gel matrix is agarose or acrylamide.